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Claims : 0 6

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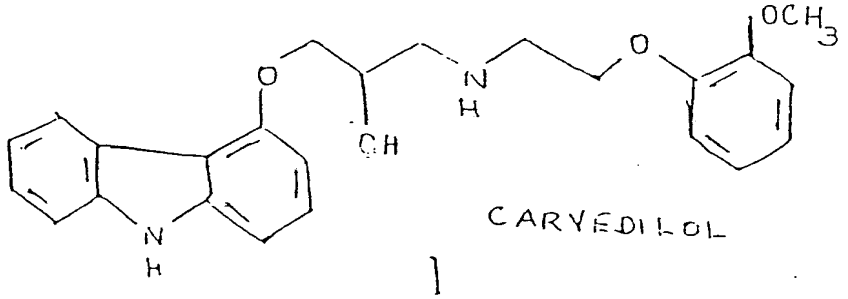
EXAMINER : DR.RUCHI TIWARI

(54) Title : AN IMPROVED PROCESS FOR THE MANUFACTURE OF CARVEDILOL.

(57) Abstract :

An improved process for the manufacture of Carvedilol of the formula I



CARVEDILOL

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By catalytic hydrogenation of N substituted Carvedilol of formula VI

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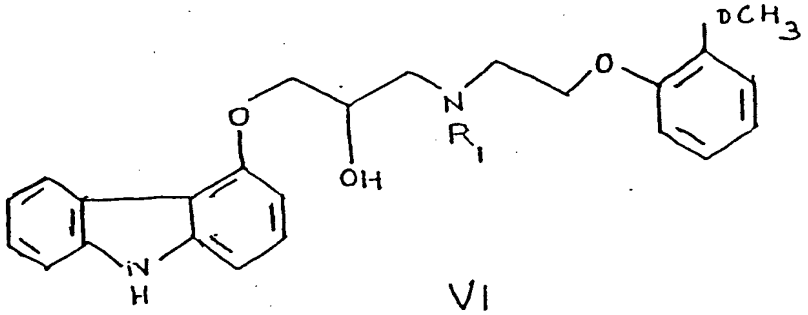
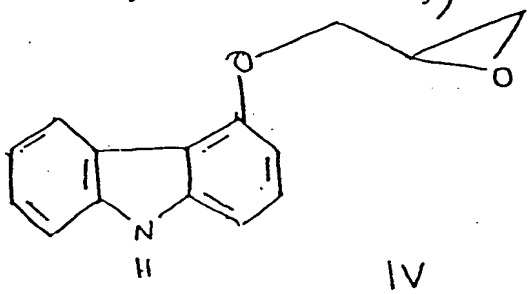


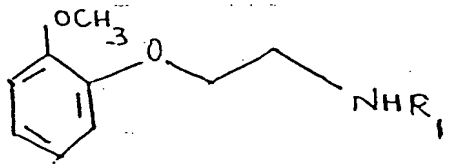
VI

(Where R1=benzyl or substituted benzyl) formed by reacting Carbazole of formula IV



IV

With substituted amine of formula V



V

Wherein R1 is as described above.

FORM – 3A

THE PATENTS ACT, 1970

COMPLETE
SPECIFICATION

SECTION 10

TITLE : AN IMPROVED PROCESS FOR THE MANUFACTURE OF CARVEDILOL.

APPLICANT : M/s. CIPLA LTD., MUMBAI CENTRAL, MUMBAI-400 008. MAHARASHTRA, INDIA

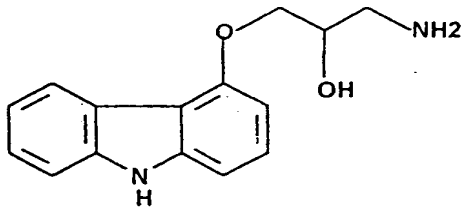
The following Specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed : -

This invention relates to an improved method for the synthesis of Carvedilol, a method which includes an elegant process for the synthesis of Carvedilol by hydrogenolysis of benzyl carvedilol.

PRIOR ART

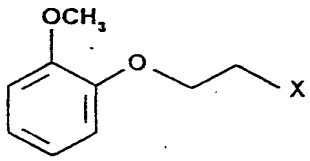
The synthesis of Carvedilol, a potent antihypertensive is described in U.S. Patent 4,503,067 and equivalent EP 0,004,920.

The processes claimed in these patents describe a method where a compound of formula II



II

is reacted with a compound of the formula III

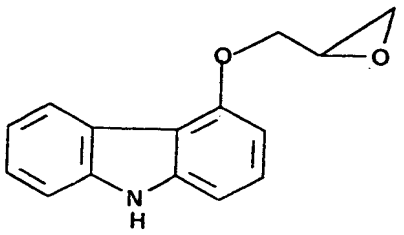


III

where X is halogen or toluene sulfonyl group

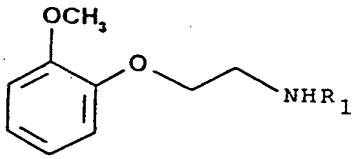
OR

A compound of the formula IV



IV

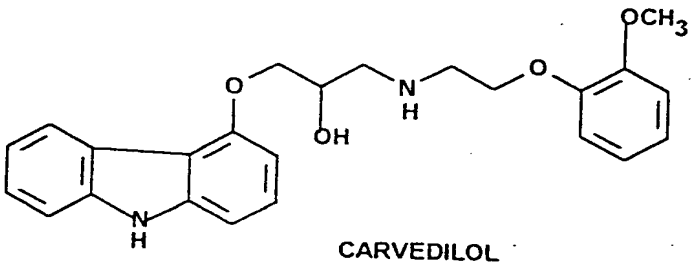
is reacted with a compound of the formula V.



V

where R_1 = H

To give Carvedilol as shown in formula I



CARVEDILOL

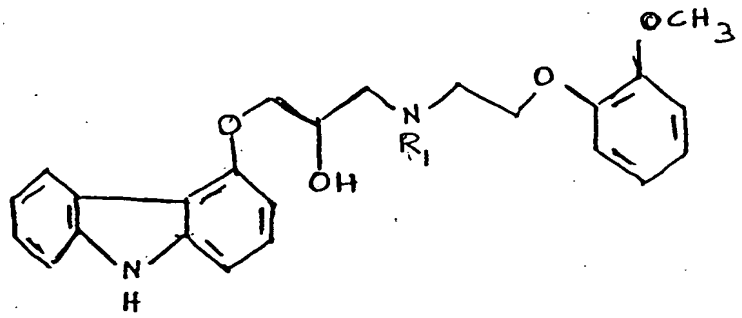
I

However these processes suffer from major disadvantages. Since the amino compounds of formula II or V cannot be used in large excess, the products obtained by these processes are contaminated with impurity in the form of dimers.

Hence repeated purifications are required to be done which affects the yield of the product.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to an elegant process for the synthesis of Carvedilol. More particularly the invention relates to synthesis of the compound of formula VI.



VI

Where R1 is benzyl or substituted benzyl group.

The compounds of formula VI are obtained by reacting a compound of the formula IV, as given herein before,

With a compound of the formula V, as given herein before, where R1 = benzyl or substituted benzyl group.

The compounds of the formula VI are further converted to the Carvedilol by catalytic hydrogenation.

The compounds of the formula V (R1 = benzyl) can be prepared by heating compound of formula V (R1=H) with benzyl chloride or substituted benzyl chloride.

Alternatively, the compounds of formula V (R1=benzyl or substituted benzyl) can be prepared by reacting a compound of the formula III, as given herein before, where X = Cl or Br, with benzyl amine.

A particular embodiment of the invention is described.

Compounds of the formula III where X = Cl or Br is reacted with benzyl amine to obtain a compound of the formula V where R_1 = benzyl. These are isolated either in their free base form or as hydrochloride or hydrobromide salts.

The substituted amine of the formula V is then reacted with 4(2,3-epoxy propoxy)-carbazole to obtain N-substituted Carvedilol of the formula VI. The solvent used in this reaction can be selected from methanol, ethanol, isopropanol, ethyl acetate, toluene or tetrahydrofuran.

The reaction is typically carried out at temperatures ranging from ambient to about 120°C for about 2 to 10 hours.

More particularly the reaction is carried out in an alcoholic solvent at reflux temperature for about 3 to 5 hours.

The N-substituted Carvedilol of the formula VI is then catalytically hydrogenated using palladium on carbon 5% using solvents selected from methanol, ethanol, isopropanol, ethyl acetate, acetone or tetrahydrofuran at temperatures ranging from ambient to about 80°C and at pressures ranging from atmospheric to about 3 kg/cm^2.

More particularly the hydrogenation can be carried out in alcoholic solvent using 5% palladium on carbon at pressure of 1 to 2 kg/cm^2

It is thus possible by way of the present invention to provide a commercially useful process for preparation of Carvedilol and its precursor in good yield and purity in a cost effective manner than that of the prior art.

The present invention is illustrated in detail with respect to the following non-limiting examples.

Example 1.

Synthesis of N[2-(2-methoxy phenoxy) ethyl] benzene methane amine.HCl.

To a solution of benzyl amine 9.2 g. (0.086 mole) in toluene (30 ml) was added 2-[2-methoxy phenoxy] ethyl bromide, 10g (0.043 mole) in isopropyl alcohol 10 ml at room temperature. The mixture was stirred for 2 hours and concentrated under vacuum. The residue was taken up in water (20 ml) and ethyl acetate (30 ml). The ethyl acetate layer was acidified to pH 3 using a 20% solution of hydrogen chloride gas in isopropanol to isolate the title compound 5.2 g (4%) as a white crystalline solid.

Example 2.

Synthesis of 1-(Carbazole-4-yloxy)-3-[[2-[2-methoxy phenoxy]ethyl] [phenyl methyl] amino]-2-propanol.

To a stirred solution of 4-(2,3-epoxy propoxy)carbazole 4.78 g (0.02 mole) in dry ethanol 50 ml, was added N – [2-(2-methoxy phenoxy)ethyl] benzene methanamine.HCl 7.34 g (0.025 mole) and triethylamine 2.52 g (0.025 mole) and the mixture heated to reflux and maintained for 4 hours. Ethanol was then distilled off and the residue taken up in water 25ml & ethyl acetate 30 ml. The ethyl acetate layer was separated and concentrated to obtain the title compound 9.8 g (98%)

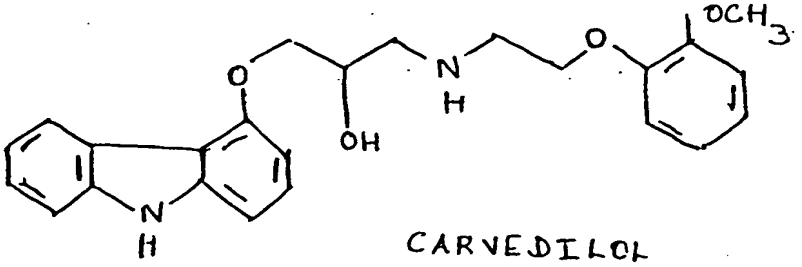
Example 3.

Synthesis of 1-(–9H Carbazole-4-yloxy)-3-[[2-(2-methoxy phenoxy) ethyl) amino]-2-propanol.

The title compound of example 2 9.8 g (0.02 mole) was taken in isopropanol 100 ml. Palladium on carbon 5%, 0.5 g was added and the mixture was taken in an autoclave and subjected to hydrogenation at a pressure of 2 kg / cm^2 for 4 hours. The catalyst was filtered off and the solvent was distilled to 30% of the original volume. The contents were chilled overnight to obtain the title compound 7.2 g as off-white crystals. The product was recrystallized from ethyl acetate to get 6.1 g (77.5%) of carvedilol as white crystals.

We claim :

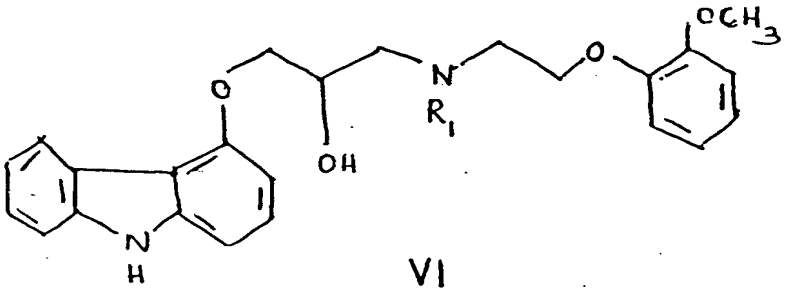
1. An improved process for the manufacture of Carvedilol of the formula I



CARVEDILOL

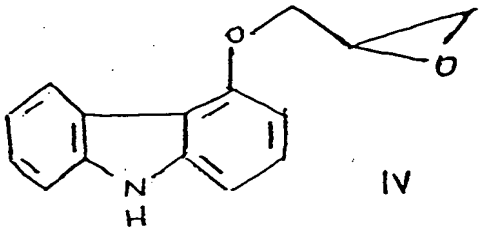
I

By catalytic hydrogenation of N substituted Carvedilol of formula VI



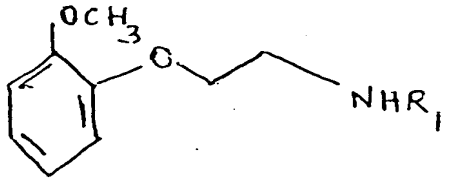
VI

(Where R1=benzyl or substituted benzyl) formed by reacting Carbazole of formula IV



IV

With substituted amine of formula V



V

Wherein R1 is as described above.

2. An improved process as claimed in claim 1, wherein the reaction is done in solvents selected form methanol, ethanol, isopropanol, ethyl acetate, toluene or tetrahydrofuran.

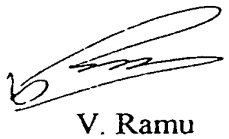
3. An improved process as claimed in claim 1, wherein the reaction temperature ranges form ambient to 120*C.

4. An improved process as claimed in claim 1, wherein the hydrogenation is carried out in solvent selected from methanol, ethanol, isopropanol, acetone, ethyl acetate or tetrahydrofuran.

5. An improved process as claimed in claim 1, wherein the hydrogenation is carried out at pressure ranging from the atmospheric pressure to about 3 kg/cm2.

6. An improved process as claimed in claim 1, wherein the hydrogenation is carried out at temperature from ambient to about 80*C.

Dated this 16th day of August, 1999.



V. Ramu

Agent for the Applicant.

(Patent Agent)